Original Article

MEDICINE PALLIATIVE CARE

DOI: 10.47582/jompac.1365715

J Med Palliat Care. 2023;4(6):619-624

Comparison of low dose cytosine arabinoside, azacitidine and azacitidine venetoclax combination treatment as remission induction in elderly acute myeloid leukemia patients

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Cite this article as: Can F, Yıkılmaz A, Gökçe D, et al. Comparison of low dose cytosine arabinoside, azacitidine and azacitidine venetoclax combination treatment as remission induction in elderly acute myeloid leukemia patients. *J Med Palliat Care*. 2023;4(6):619-624.

Received: 25.09.2023 ◆ **Accepted**: 17.11.2023 ◆ **Published**: 31.12.2023

ABSTRACT

Aims: Low-intensity therapies are widely preferred in the treatment of advanced age, fragile acute myeloid leukemia (AML) patients. In this study, we aimed to compare hematological recovery rates after first cycle chemotherapy and overall survival for advanced aged AML patients treated with azacitidine (AZA) or low dose cytosine arabinoside (LDCA) or venetoclax (Ven) with AZA combination.

Methods: Ninety-one patients were retrospectively analyzed.

Results: Forty-one patients treated with LDCA, 30 patients treated with AZA and 20 patients treated with AZA+Ven were included in the study. Patients who received these three treatments and who achieved response and did not receive any other treatment during the follow-up period were included in the study. Median age at diagnosis was 70. The percentage of patients who achieved neutrophil recovery after the first cycle was 27%, 73% and 50% of the patients treated with LDCA, AZA and AZA+Ven respectively. The rate of patients who achieved platelet recovery was 60%, 80%, 70% respectively. Erythrocyte transfusion independency was 54% for LDCA patients, 73% for AZA patients and 60% for combination therapy. Overall survival was longer in patients receiving AZA+Ven than other treatment groups while grade 3-4 infections were more common in the first cycle of the treatment.

Conclusion: According to our study, patients treated with AZA had better platelet and neutrophil recovery rates with also longer overall survival than patients treated with LDCA, but total overall survival was superior in AZA+Ven combination. Hypomethylating agents with venetoclax is a preferable treatment option in elderly AML patients.

Keywords: Acute myeloid leukemia, azacitidine, low dose cytosine arabinoside, venetoclax, elderly patients

INTRODUCTION

Acute myeloid leukemia (AML) is a clonal malignant disease characterized by the presence of abnormal leukemic cells in the bone marrow or soft tissues. Median age is 68 and prevalence of the disease increases with age.[1] Premalignant clonal hematopoiesis can be observed in 2 % of normal healthy individuals, and 5-6 % of individuals older than 70 years. This may be an explanation for the increase in AML incidence in advanced age.[2] According to the SEER data; disease-related death in AML patients within first year is 80 % over the age of 65 and it is one of the lowest survival cancer types with a median survival of 2.7 months.[3]

Anti-leukemic therapy is essential for all AML cases regardless of age and treatment should be selected to the patients' performance status and comorbid conditions.[4] There are publications showing that treatment-related mortality in AML cases varies between 10-30%. It has been reported that one fourth of newly diagnosed AML cases who are not suitable for anti-leukemic treatment were treated with hypomethylating agents (HMA). In advanced age, this rate increases up to 60%.[5]

For nearly 30 years; LDCA has been used as a treatment option for acute leukemia patients with advanced age and/or comorbidities who are not suitable for intensive chemotherapy. For AML cases over 70 years old; studies comparing LDCA with the best supportive care approaches and hydroxyurea showed that LDCA was more beneficial.[6,7] After that, LDAC have remained the main therapy in AML patients with advanced

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age in comparison studies with new drugs. With the demonstration of the effectiveness of hypomethylating agents decitabine and azacitidine (AZA) in AML in the mid-2000s, these agents became a therapeutic option for AML treatment. AZA (75 mg / m² day, 7 days) was found to achieve a longer overall survival (OS) compared to LDAC, intensive induction therapy or best support care, although it was statistically insignificant.[5,8,9] After the use of HMA treatments alone, the addition of venetoclax (ven) to this treatment resulted in an improvement in OS in patients who were elderly, frail and unsuitable for intensive treatment.[10,11] In recent years, adding ven therapy to HMA has become the gold standard option in treatment for patients in this age group.[12,13] Unfortunately, ven+hypomethylating agent treatments, which are now recommended as gold standart therapy in many guidelines for older AML patients, can only be used with off-label approval in our country due to reimbursement institution restrictions.

Despite advances in treatment, disease-related and treatment-related delayed hematological recovery, febrile neutropenia, bacterial and viral infections are the main problem staying beyond the mortality for these patients. In this study we aimed to compare the clinical results of LDCA, AZA, AZA+Ven treatments in patients with advanced age AML followed in our center.

METHODS

The study was carried out with the permission of the Ankara Yıldırım Beyazıt University Ethics Committee (Date: 14/01/2021, Decision No: 67). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patients

Ninety-one patients diagnosed with de-novo AML were included in the study. AML cases 60 years and older who received the first induction chemotherapy and achieved a response were included. The diagnosis of AML was made according to World Health Organization (WHO) and European Leukemia Network (ELN) classifications.

Data Collection

Study was designed retrospectively by using file data records of patients whose diagnosis and treatment were performed in our center.

Age, gender, Eastern Cooperative Oncology Group (ECOG) performance status, treatment groups, neutrophil and platelet recovery times, eritrocyte indepency status after first cycle, duration of induction therapy, hospitalization days, bone marrow pathological findings, hemogram, biochemical parametres were recorded.

The aim of the study was to evaluate to compare hematological recovery rates, infective complication rates after first cycle chemotherapy and overall survival so in order to prevent bias, patients who received one of the three treatment arms in the study and achieved a complete response, complete response with partial hematologic recovery, complete response with incomplete recovery, morphologic leukemia free state and partial remission according to the ELN 2022 response criteria at the end of the first cycle and continued their treatment with the same chemotherapy were enrolled. Again, in order to avoid bias, patients who did not respond to their first treatment and/or switched to another treatment were excluded from the evaluation. ELN 2022 response criteria was shown in **Table 1**.

Infection grading was based on the adverse events grading of the National Cancer Institute.[14] After the first chemotherapy cycle; the neutrophil recovery time was calculated as the day when the absolute neutrophil count was ≥500×10⁶/L for 3 consecutive days. For platelet count, recovery time was calculated as the day which platelet count was ≥50,000×10⁶/L in days for 3 consecutive days. Since these values are the hematological recovery values in ELN 2022, these numbers were taken as basis.[12] Since there was no clear limit for hemoglobin recovery, erythrocyte transfusion independence was evaluated at the end of the first cycle. Drug dose and days were compatible with the previous studies; low dose subcutaneous LDCA was administered as 20 mg twice daily for ten days; subcutaneous AZA was administered 75 mg/m²/day for seven days.[15,16] In AZA treatment

Table 1. ELN 2022 response criteria

Response	Criterias
Complete response (CR)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease; neutrophil count ≥1000×10⁶/L; platelet count ≥100,000×10⁶/L
Complete response with partial hematologic recovery (CRh)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease with neutrophil count 500-1000×10⁶/L and platelet count 50,000-100,000×10⁶/L
Complete response with incomplete recovery (CRi)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease with neutrophil count <1000×10⁶/L or platelet count <100,000×10⁶/L
Morphologic Leukemia Free State (MLFS)	Bone marrow blasts <5%; no circulating blasts; no extramedullary disease regardless of hematological recovery
Partial remission (PR)	Bone marrow blast 5-25 % and at least 50 % blast decrease in bone marrow after treatment with neutrophil count ≥1000×10⁶/L; platelet count ≥100,000×10⁶/L

group, the 5-2-2 scheme was widely used due to a two-day break at the weekend.[17] AZA and ven combination was administered as in the clinical trials.[10,11] Azacitidine 75 mg/m²/day were given for 7 days and ven 100 mg on the 1st day, 200 mg on the 2nd day and 400 mg on the 3rd day. Ven was given in all subsequent 28-day cycles. In patients given azole prophylaxis, the ven dose was given as 100 mg. Treatment cycles were scheduled every 4 weeks for all drugs until progression, relapse or intolerance.

Statistical Analysis

Statistical analysis "IBM SPSS Statistics for Windows. It was performed using Version 25.0 (Statistical Package for the Social Sciences, IBM Corp., Armonk, NY, USA). Descriptive statistics are presented as n and % for categorical variables and as Mean±SD and median (IQR) for continuous variables. Chi square test was used to compare mortality with various treatment parameters. The normal distribution assumptions of the data were examined by looking at the Kolmogorov-Smirnov values. One Way ANOVA test and Kruskal Wallis H test were used for comparisons between groups, and Paired Samples t test and Wilcoxon Signed Ranks Test were used for comparison of repeated measurements. In cases where significant differences were found as a result of One Way ANOVA test and Kruskal Wallis H test, Sidak Post-Hoc test was used to determine the direction of the difference. $p<0.05$ was considered statistically significant.

RESULTS

The data of 91 cases with denovo AML were evaluated. 41 patients were treated with LDCA, 30 patients with AZA, 20 patients with AZA+ven. There was no difference between the two treatment arms in terms of gender, age, hemogram parameters, bone marrow blast percentages at the time of diagnosis. The number of ECOG 3-4 patients was higher in the LDAC arm than in the AZA and combination therapy groups. In Table 2, clinical and laboratory findings at the time of diagnosis were shown according to the treatment protocol.

After the first month of the therapy, number of patients having an absolute neutrophil count above 500×10^6/L and platelet count above $50,000\times10^6$/L was significantly lower in LDCA therapy arm. Although the number of patients became erythrocyte transfusion independent was lower in LDCA group from the other therapy groups, this difference didn't have a statistically significance. Grade 3-4 infection during the first month of the therapies was significantly higher in LDAC and combination therapy groups than AZA treatment group. Percentages of patients with febrile neutropenia (FEN) was significantly higher in LDCA arm as well as duration of hospitalization and hospitalization days more than 1 week in first month of treatment. Comparison of treatment response and treatment-related complications at the first months of induction treatment were shown in Table 3.

Median OS of 91 patients was 7.1 months. Median OS of the patients who treated with LDCA treatment was 5.2 months, AZA was 9.3 months and AZA+Ven combination was 15.7 months. When stratified by age and ECOG performance status, overall survival was significantly better in patients under 70 years of age and in patients with ECOG 2 and below. This difference was statistically better in AZA+ven treatment patients. Similar to overall survival, survival in these subgroups was significantly longer in favor of AZA+ven combination therapy. Survival data are presented in Table 4.

Table 2. Clinical and laboratory findings of the patients at the time of diagnosis

	Total patients n: 91	Low dose cytosine arabinoside n:41 (45%)	Azacitidine n:30 (33%)	Azacitidine+ Venetoclax n:20 (22%)	p value	Post-hoc
Gender (F/M)	38 (42%)/53 (58%)	12 (29%)/29 (71%)	15 (50%)/15 (50%)	11 (55%)/9 (45%)	0.08	-
Age [Median (Min-Max)]	70 (60-88)	75 (65-88)	69 (65-74)	65 (60-75)	0.89	-
Hemoglobin level (Mean± SD) g/dl	9.6 (±2.03)	8.9 (±2.08)	10.3 (±1.6)	9.4 (±2.06)	0.43	-
Bone marrow blast percentage [Median (Min-Max)]	48 (20-94)	56 (24-94)	43 (20-89)	45 (30-90)	0.07	-
Leucocyte count [Median (Min-Max)]	5750×10^6/L ($200-291000$)	5780×10^6/L ($730-291000$)	6250×10^6/L ($730-113000$)	4860×10^6/L ($200-168000$)	0.08	-
Neutrophil count [Median (Min-Max)]	2580×10^6/L ($10-92800$)	2000×10^6/L ($0-92800$)	2600×10^6/L ($0-8700$)	2960×10^6/L ($20-130800$)	0.10	-
Platelet count ($x10^6$/L) [Median (Min-Max)]	58126×10^6/L ($5000-202000$)	48100×10^6/L ($7000-202000$)	52500×10^6/L ($5000-151000$)	62460×10^6/L ($8000-140000$)	0.09	-
ECOG, n (%)						
0-2	30 (33%)	5 (12%)	14 (47%)	11 (55%)	0.01	1>2,3
3-4	61 (67%)	36 (88%)	16 (53%)	9 (45%)		

F: Female, M: Male, Min: Minimum, Max: Maximum, SD: Standart Deviation, CRP: C-reactive protein, ANC: Absolute neutrophil count, ECOG: Eastern Cooperative Oncology Group

Table 3. Comparison of treatment response and treatment-related complications at the first month of induction treatment

	Total patients n: 91	Low-dose cytosine arabinoside treatment n: 41	Azacitidine treatment n: 30	Azacitidine+ venetoclax treatment n: 20	p value	Post-hoc
Patients having ANC >500×10^6/L after the first months of induction treatment	43 (47.2%)	11 (27%)	22 (73%)	10 (50%)	0.01	1<2,3
Patients who achieved transfusion independency after the first months of induction treatment	56 (61 %)	22 (54%)	22 (73%)	12 (60%)	0.13	-
Patients having >50000×10^6/L platelets count after the first months of induction treatment	62 (68%)	24 (60%)	24 (80%)	14 (70%)	0.04	1<2,3
Number of patients achieving recovery of neutrophil and platelet counts and transfusion independency after the first months of induction treatment	36 (39.5%)	8 (19.5%)	20 (66%)	8 (40%)	0.01	1<2,3
Grade 3-4 infection in first month of chemotherapy	23 (24%)	11 (27%)	5 (17%)	6 (30%)	0.02	1,3>2
Number of patients with FEN condition	36 (39.5%)	18 (44%)	10 (33%)	8 (40%)	0.04	1>2,3
Duration of hospitalization at the first chemotherapy cycle (Median)	16 days	18 days	8 days	16 days	0.04	1,3>2
Number of patients Hospitalized for more than 1 week at the first chemotherapy cycle	21 (23%)	12 (29%)	4 (13%)	5 (25%)	0.01	1,3>2

ANC: Absolute neutrophil count, FEN: Febrile neutropenia

Table 4. The comparisons of OS time according to Low dose cytosine arabinoside and 5-Azacitidine treatment of older aged AML patients

	Total patients n: 91	Low dose cytosine arabinoside n: 41	Azacitidine treatment n: 30	Azacitidine+venetoclax treatment n: 20	p value	Post-hoc
OS median (month)	7.1	5.2	9.3	15.7	0.04	3>2,1
Age adjustment OS (month)						
<70	7.4	4.1	11.9	16.3	0.02	3>2,1
≥70	5.3	5.2	5.8	12.1		
ECOG adjustment OS (month)						
0-2	12.1	8.3	12.3	17.8	0.04	3>2,1
3-4	5.8	4.2	6.1	11.3		

OS: Overall survival, ECOG: Eastern Cooperative Oncology Group

DISCUSSION

The goal in the treatment of acute leukemia is to achieve a complete response. However, the goal of achieving a complete response with intensive chemotherapies is not always a practical approach because of the comorbidities associated with AML patients and higher ECOG performance score. The treatment for these patients should be to provide survival advantage and increase in quality of life. Low-intensity protocols and supportive treatments should be personalized due to patient and disease-related factors. LDCA and HMA are frequently used low-intensity treatment options. The physical performance status of the elderly AML patients has a critical importance in their tolerance to treatment. It has been reported that treatment-related toxicity has been more common in patients with advanced age AML who have poor performance at the time of treatment and therefore treatment response has been lower from fit patients.[18] In this study including newly diagnosed de novo AML cases who had not received treatment before; it was aimed to compare the clinical and laboratory results of LDCA, AZA and AZA+Ven treatments. Of these three treatment types, HMA and ven combination can only be given to patients in our country with off-label approval. LDCA treatment was a treatment option for elderly frail AML patients for a long time until HMA treatments was developed. In comparative studies of HMA treatments with LDAC, HMA treatments were found to be more successful in this patient group.[8,9] In light of this information, in our country, HMA treatment has become the most frequently used treatment in the first line therapy of fragile AML patients who are suitable for intensive treatments. Subsequently, with the result of studies adding HMA treatments and LDCA ven, these combinations became the best choice in these patients.[10,19] In this study, which was conducted specifically to reveal the situation in our country, three treatments were compared.

Totally 91 patients; 41 treated with LDCA, 30 with AZA monotherapy and 20 with AZA+Ven therapy was analyzed. The median age of the patients is 70 and 67% of our patients had ECOG performance status 3-4, making it a suitable selected cohort for analysis.

Patients having neutrophil and platelet recovery after the first course of chemotherapy were higher in AZA monotherapy patients. This may be due to the low probability of LDCA treatment improving whole blood parameters in the first month, as expected. In terms of combination treatment, since the ven HMA combination is expected to be more successful than the single HMA treatment, the low cytopenia recovery rate at the end of the first cycle in the combined treatment may be due to ven-related cytopenia. As a matter of fact, in terms of overall

survival, it was seen that the AZA + Ven combination was more successful. It has been suggested that neutrophil recovery time is affected not only by chemotherapy but also by patient and treatment related factors.[20] In our cohort, patients who received LDCA had a higher rate of grade 3-4 infection with less neutrophil recovery rates. Another important data of the study is that grade 3-4 infections were more common in the combination arm, which is the most effective arm, and the duration of hospitalization for more than 1 week and the frequency of febrile neutropenia were found to be higher in the combination treatment than in the HMA monotherapy arm. The longest patient hospital stays in the LDCA arm may be due to the fact that this patient group received treatment for a longer period of time (7 days versus 10 days) and consisted of patients with higher ECOG. Again, prolonged cytopenias in this treatment arm may explain the higher rate of grade 3-4 infections and FEN. In combination therapy patient group, the longer hospital stay compared to monotherapy, due to follow-up for tumor lysis after rump up in the first cure, and the prolonged cytopenic state due to ven may explain the increased frequency of grade 3-4 infections and FEN compared to monotherapy. According to the data of comparing azacitidine and low dose cytarabine in terms of intravenous antibiotic requirement involving 131 patients; It was shown that less antibiotics were needed in the azacitidine group.[9] The hospitalization periods of the patients who received azacitidine and best supportive care, low dose cytarabine and intensive chemotherapy were compared; the average length of hospital stay in the azacitidine arm was 20.7 days per year, while in the others it was reported as 31.6 days. Also; the hospitalization time per year was significantly less in treated patients with azacitidine when it was compared with all three groups separately.[9] In our study, compatible with the literature; hospitalization periods longer than 1 week in the first month patients treated with AZA were found to be lower than other treatment groups and the rates of febrile neutropenia and grade 3-4 infection were also lower. Despite these side effects and long hospital stay, overall survival of patients receiving treatment with the combination was found to be better in the overall analysis. It has been reported that in patients over 65 years of age, azacitidine provides a survival advantage of 12.1 months versus 6.9 months compared to low dose cytarabine, intensive induction chemotherapy or best supportive chemotherapy.[8] Study in the literature that enabled the combination to be approved in world showed an approximately 5-month survival advantage with the addition of ven to azacitidine treatment 14.7 months vs 9.6 months.[10] In our study, combination therapy was shown to have an overall survival advantage of 10.3 months compared to LDCA treatment and 6.4 months compared to single azacitidine treatment.

Limitations of the study

The limitations of our study are that it has a relatively limited number of patients and it is a single center data.

CONCLUSION

Considering the difficulties of treatment for elderly and fragile AML patients, our study is important due to the evaluation of hospitalization, infection status and hematological recovery during/after the first course of low-dose chemotherapy, HMA and HMA ven combination therapy. Which is not yet covered by payment in our country and can be used with an off-label approval, but which is a standard treatment all over the world, ven+AZA treatment provided better survival to elderly frail patients than LDAC alone and AZA treatment alone.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of the Ankara Yıldırım Beyazıt University Ethics Committee (Date: 14.01.2021, Decision No: 67).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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